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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/513,024	Applicant(s) VILEN ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *12-14,20,23-29,32 and 34-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 15-19, 21-22, 30-31, and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. The instant application is in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

2. Applicant's election with traverse of claims 1-33 (Group I) with a species election of i)B cell receptor, ii) dissociation of components, iii) antibody, iv) Ab to transducer component, v) Ig-α, vi) autoreactive B cell, vii) SLE, viii) FcεRI, ix) mast cell, and x) *in vivo,* in Paper No. 7 is acknowledged.

A) Restriction election:

The traversal with respect to the restriction election is on the ground(s) that a search for Group I would be sufficient to examine the claims of Groups III and IV as well. This is not found persuasive because as set forth in Paper No.6, each method differs with respect to ingredients, method steps, and endpoints. An assessment of the patentability of a method to desensitize a receptor does not address the issues of patentability associated with a method to identify compounds useful for desensitizing a receptor or a method to sensitize a receptor.

The requirement is still deemed proper and is therefore made FINAL.

B) Species election:

The traversal with respect to the species election is in general on the grounds that a search of the generic claims would be sufficient to examine all claims. With the exception of groups ii) and v) as addressed below, this is not found persuasive for the reasons of record in Paper No. 6.

The requirement of a species election between dissociation of the components vs. inhibition of association of the components is traversed on the grounds that the distinction is not meaningful with respect to a search of the prior art, as is the requirement of a species election between Igα and Igβ.

After a more detailed review of the prior art, the examiner agrees that in these two cases the search of the prior art is co-extensive. With respect to the distinction between Igα and Igβ, it is also noted that the prior art supports Applicant's argument that although they are structurally distinct molecules, Igα and Igβ function together to form the transducer component in most, if not all, physiologically relevant instances.

The species requirement with respect to groups ii) and v) is hereby withdrawn.

The requirement with respect to groups i), iii), iv), and vi)-x) is still deemed proper and is therefore made FINAL.

3. Given the previous restriction/election of species requirement, which is hereby reiterated; claims 34-49 have been withdrawn from consideration by the examiner under 37 CFR 1.142(b), as being drawn to a nonelected invention; claims 12-14, 20, 23-28, 29, and 32 have been withdrawn from consideration by the examiner under 37 CFR 1.142(b), as being drawn to nonelected species.

Claims 1-11, 15-19, 21-22, 30-31, and 33 *are under consideration in the instant application.*

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, *with respect to the non-elected species* of an NK cell receptor, the provisional application upon which priority is claimed fails to provide written description under 35 U.S.C. 112 for claim 1 and dependent claims of this application *only with respect to the non-elected species of NK cell receptor*.

5. The file jacket indicates that two IDS's, (Paper Nos. 3 and 4) were filed 6/18/00 and 6/19/00; however neither a PTO-1449 nor reference copies appear in the instant application. Applicant is invited to resubmit appropriate documentation to complete the instant file. The examiner apologizes for the inconvenience to Applicant for having to resubmit such documentation.

6. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required if the application is allowed.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. For examination purposes the following is noted:

in the interest of compact prosecution the non-elected embodiments have been included in the analyses under the first paragraph of 35 U.S.C. 112 where appropriate; and

in instances where the prior art references are also applicable to certain non-elected species, these non-elected embodiments have also been included under 35 U.S.C. 102 when deemed appropriate.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-6, 15-19, 21-22, and 30-33 (as well as non-elected claims 20, 23-29, and 32) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to desensitize a receptor by administering the specific regulatory compounds disclosed on pages 36-37 and the mAbs disclosed in Example 9, does not reasonably provide enablement for a method to desensitize a receptor by administering the broad class of a "regulatory compound". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies such "regulatory compounds" other than those encompassed by the specific examples set forth on pages 36-37, and in Example 9. Thus while a "regulatory compound" that binds the extracellular ligand binding component or the transducer component may have some notion of the activity of the claimed compound; there is insufficient biochemical or structural information to enable the skilled artisan to make and use the regulatory compound as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

In addition, the *in vivo* application of a "regulatory compound" is fraught with technical difficulties. Pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the technical difficulties associated with *in vivo* therapies, the skilled artisan would be faced with undue experimentation in determining which regulatory compounds could be utilized *in vivo*.

Furthermore, Applicant has not provided sufficient objective evidence that in vitro assays such as inhibition of intracellular calcium flux (e.g., as disclosed on page 54 of the specification as-filed) are reasonably predictive of *in vivo* immunosuppressive activity. Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 1992, vol. 4, page 553-560; see in particular page 558, column 2).

Thus the specification does not provide a sufficient enabling description of the claimed invention. A person of skill in the art is not enabled to make and use a representative number of "regulatory compounds" as encompassed by the full breadth of the claim as currently recited. There is insufficient guidance in the specification as-filed to direct a person of skill in the art in how to make and use *any* "regulatory compound", other than antibodies and the specific examples on pages 36-37 of the specification. The term "regulatory compound" as recited encompasses *any* regulatory compound. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Since it is unpredictable as to which other regulatory compound would have the recited activity of desensitizing a receptor; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

11. Claims 1-6, 15-19, 21-22, 30-31, and 33 (as well as non-elected claims 12-14, 20, 23-29, and 32) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite a "regulatory compound" that causes the dissociation of, or inhibits the association of, the extracellular ligand binding component and the transducer component as part of the invention.

The specific regulatory compounds which bind to the extracellular ligand binding domain, as described on pages 36-37 of the specification as-filed, have adequate written description; as do antibodies to structurally conserved regions of the extracellular ligand binding component (e.g., anti-μ mAb); and mAbs 32 and 172 which bind to the transducer components Igα/Igβ.

However, there is insufficient written description as to:

regulatory compounds that bind to the antigen binding region of the extracellular ligand binding component *other than those specific examples found on pages 36-37* of the specification as-filed *for BcR*;

regulatory compounds *other than antibodies* that bind the transducer component; and

regulatory compounds which bind to transducer components *other than* Igα and Igβ.

"Regulatory compound" encompasses a substantial variety of subgenera that can be any of a variety of classes of compounds (e.g., antibody versus a lipid-based compound, page 18 of the specification as-filed). A description of a genus of regulatory compounds may be achieved by means of a recitation of a representative number of regulatory compounds falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The instant disclosure of a specific antigen (NP_7BSA), a specific peptidomimetic (SEQ ID NO:1), and an antibody to the extracellular ligand binding component does not adequately describe the scope of the claimed genus of regulatory compounds that bind the extracellular ligand binding component. Each extracellular ligand binding component is structurally distinct because each BcR/mIg binds a distinct antigen. Thus, a disclosure of a particular regulatory compound that binds the extracellular ligand binding component at the same site as antigen is only relevant for a BcR of a particular antigen specificity. Consequently, although several classes of compounds are disclosed, they are relevant only to the BcR bearing a particular specificity; and so in this particular situation a representative number of examples falling within the scope of the genus has not been provided.

Likewise, the instant disclosure of two mAbs which bind the transducer components Igα or Igβ, mAb32 and mAb 172, does not adequately describe the scope of the claimed genus of regulatory compounds that bind the transducer component since transducer components *other than* Igα/Igβ are used by other receptors to transmit signals for distinct biological activities.

In addition, although mAbs 32 and 172 are disclosed in Example 9 as binding to "Igα/Igβ ECD"; it is unclear whether Igα *or* Igβ is bound, or to what *specific region* of Igα/Igβ mAb 32 or mAb 172 bind. Since no examples appear to be disclosed of regulatory compounds that *selectively bind* a portion of the transducer component, as recited in claims 5 and 6; there appears to be insufficient written description to support these claim limitations in the specification as-filed.

Finally, there is insufficient written description of an antibody that is bi-specific (non-elected). Although some suggestion is given of potential targets for the second specificity of the bispecific antibody on page 22 of the specification as-filed; adequate written description requires more than a mere statement that it is part of the invention. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Therefore, only the specific examples on pages 36-37 of the specification as-filed and the antibodies disclosed in Example 9 that bind the transducer components Igα/Igβ, but not the full breadth of the claim that further comprises "regulatory compounds" in general, meet the written description provision of 35 U.S.C. 112, first paragraph. In addition, Applicant has not provided adequate written description for additional limitations with respect to the site on the Igα/Igβ transducer component bound by the antibodies. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Alternatively, Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 3-4, 7-8, 10, 15-16, 18 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Cambier et al. (Proc. Natl. Acad. Sci. USA 1988 85:6493-6497, see entire document).

Cambier et al. teach a method to desensitize a receptor by contacting said receptor with a regulatory compound wherein the regulatory compound causes a dissociation of and/or inhibits the association of the extracellular ligand binding component and the transducer component (see entire document, especially the "Discussion"), wherein:

the receptor is a B cell antigen receptor (BcR) (i.e., mIg, e.g., "Abstract");

the regulatory compound binds the extracellular ligand binding component (i.e., mIg, e.g., "Abstract");

the regulatory compound is an antibody (i.e., anti-IgD/IgM, e.g., Figure 2);

the antibody is divalent (e.g., page 6494, 2nd column, end of 1st paragraph of "Results");

the transducer component is Igα/Igβ (Igα/Igβ are the intrinsic transducer component of the BcR);

the extracellular binding component comprises IgD or IgM (e.g., Figures 1 and 2); and

the regulatory compound is contacted with the receptor in an in vitro assay (e.g., "Methods").

Although Cambier et al. do not address the molecular basis for the receptor desensitization as encompassed by the claim limitations, Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property, such as the detailed mechanism by which receptor desensitization occurs or the molecular components involved. The claimed functional limitations of causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component would be inherent in a method to desensitize a receptor, especially when the same receptor (BcR) and the same regulatory compounds (anti-Ig antibodies) are employed in that method.

The burden is on Applicant to establish a patentable distinction between the claimed and referenced methods. See MPEP 2112 - 2113.

Similarly, when claims recite using an old composition or structure (e.g. anti-Ig (anti-BcR) antibodies) and the method of use is directed to a result or property of that composition or structure (i.e., causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component), then the claims are anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

14. Claims 1, 3-4, 7, 15-16, 18, 21 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Vilen et al. (J. Immunol. 1996 159:231-243, see entire document).

Vilen et al. teach a method to desensitize a receptor by contacting said receptor with a regulatory compound wherein the regulatory compound causes a dissociation of and/or inhibits the association of the extracellular ligand binding component and the transducer component (see entire document, especially the "Discussion"), wherein:

the receptor is a B cell antigen receptor (BcR) (e.g., "Abstract");

the regulatory compound binds the extracellular ligand binding component (i.e., antigen, e.g., "Abstract");

the regulatory compound is a mimetope of a peptide(i.e., the antigen-mimetic sequence 3-83ag1, e.g., see page 237, last paragraph);

the transducer component is Igα/Igβ (Igα/Igβ are the intrinsic transducer component of the BcR);

the extracellular binding component comprises IgD or IgM (i.e., the μδ of the 3-83 μδ Ig transgenic B cells, e.g., Figure 10);

the BcR selectively binds to an antigen associated with a graft cell (i.e., anti-H-2K^k, see page 237, last paragraph);

the receptor is expressed by a cell that is

a B cell lymphoma (e.g., the K46 lymphoma, see "Cells, page 232 and Figures 1-9); and

the regulatory compound is contacted with the receptor in an in vitro assay (e.g., "Methods").

Although Vilen et al. do not teach that dissociation/inhibition of association is the mechanism underlying the molecular basis for the receptor desensitization as encompassed by the claim limitations, Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property, such as the details of the mechanism by which receptor desensitization occurs. The claimed functional limitations of causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component would be inherent in a method to desensitize a receptor, especially when the same receptor (BcR) and the same regulatory compounds (peptide mimetics) are employed in that method.

The burden is on Applicant to establish a patentable distinction between the claimed and referenced methods. See MPEP 2112 - 2113.

Similarly, when claims recite using an old composition or structure (e.g. a peptide mimetic that binds the extracellular ligand binding component of the BcR) and the method of use is directed to a result or property of that composition or structure (i.e., causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component), then the claims are anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

15. Claims 1-2, 4-8, 10-11, 15-18 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al. (Int. J. Hematol. 1996 64:39-46, see entire document).

Nakamura et al. teach a method to desensitize a receptor by contacting said receptor with a regulatory compound wherein the regulatory compound causes a dissociation of and/or inhibits the association of the extracellular ligand binding component and the transducer component (see entire document, especially the "Discussion"), wherein:

the receptor is a B cell antigen receptor (BcR) (e.g., "Abstract");

the regulatory compound binds the Igβ transducer component (e.g., "Abstract": note that CD79b is another name for Igβ);

the regulatory compound is a divalent antibody (i.e., anti-Igβ/CD79b, e.g., "Title");

the extracellular binding component comprises IgD or IgM (e.g., Figure 2); and

the regulatory compound is contacted with the receptor in an *in vitro* assay (e.g., "Methods")

Although Nakamura et al. do not address the molecular basis for the receptor desensitization as encompassed by the claim limitations, Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property, such as the mechanism by which receptor desensitization occurs. The claimed functional limitations of causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component would be inherent in a method to desensitize a receptor, especially when the same receptor (BcR) and the same regulatory compounds (anti-Igβ/CD79b antibodies) are employed in that method.

The burden is on Applicant to establish a patentable distinction between the claimed and referenced methods. See MPEP 2112 - 2113.

Similarly, when claims recite using an old composition or structure (e.g. anti-Igβ/CD79b antibodies) and the method of use is directed to a result or property of that composition or structure (i.e., causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component, including by binding to specific sites on the transducer component), then the claims are anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Finally, a teaching of an antibody that does not explicitly indicate a non-divalent form of the antibody is immediately envisaged to mean that the antibody is divalent, since IgG1 antibodies such as the anti-CD79b antibody of Nakamura et al. are divalent unless modified. Therefore the claim limitation of "divalent" is also anticipated. (See In re Schaumann, 572 F.2d 312, 197 USPQ 5 (CCPA 1978)).

16. Claims 1, 3-4, 7-8, 10, 15-16, 18-19, 21-22, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. (Int. Archs. Allergy Appl. Immunol. 1982, vol. 69:269-301, see entire document).

Suzuki et al. teach a method to desensitize a receptor by contacting said receptor with a regulatory compound wherein the regulatory compound causes a dissociation of and/or inhibits the association of the extracellular ligand binding component and the transducer component (see entire document, especially the "Discussion"), wherein:

the receptor is a B cell antigen receptor (BcR) (e.g., "Abstract");

the regulatory compound binds the extracellular ligand binding component (i.e., the "Fab", e.g., "Abstract");

the regulatory compound is an antibody (e.g., "Abstract");

the antibody is divalent (e.g., "Abstract");

the transducer component is Igα/Igβ (Igα/Igβ are the intrinsic transducer component of the BcR);

the extracellular binding component comprises IgD or IgM (e.g., page 300, 4th full paragraph);

the BcR binds an antigen associated with the autoimmune disease SLE (see entire document);and

the regulatory compound is contacted with the receptor in an in vitro assay (e.g., "Methods").

Suzuki et al. teach that treatment of B cells (derived from PBL) from normal and SLE patients with antibody to the BcR (anti-Fab) results in what they term an "inhibitory effect" on antibody secretion by the B cells (see abstract). Suzuki et al. do not explicitly teach that the "inhibitory effect" they observe encompasses receptor desensitization, as recited in the preamble of the claims. However, Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention.

Similarly, Suzuki et al. do not address the mechanism underlying the molecular basis for the "inhibitory effect". However, Applicant is reminded that the courts have held that there is no requirement that those of ordinary skill in the art know of an inherent property, such as the details of the mechanism by which receptor desensitization occurs. The claimed functional limitations of causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component would be inherent in a method that results in an "inhibitory effect" on antibody production, especially when the same receptor (BcR) and the same regulatory compounds (antibodies to the BcR in the form of anti-Fab) are employed in that method.

The burden is on Applicant to establish a patentable distinction between the claimed and referenced methods. See MPEP 2112 - 2113.

When claims recite using an old composition or structure (e.g. antibodies that bind the extracellular ligand binding component of the BcR) and the method of use is directed to a result or property of that composition or structure (i.e., causing a dissociation of and/or inhibiting the association of the extracellular ligand binding component and the transducer component), then the claims are anticipated. See MPEP 2112.02. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-2, 4-11, 15-19, 21-22, 30-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ways et al. (US Pat. No. 6,103,713) in view of Nakamura et al. (Int. J. Hematol. 1996 64:39-46), and in further view of Vilen et al. (J. Immunol. 1996 159:231-243).

The claims are drawn to therapeutic methods of desensitizing an autoreactive B cell receptor in patient with the autoimmune disease SLE by contacting the receptor with a regulatory compound that causes a dissociation of and/or inhibits the association of the extracellular ligand binding component and the transducer component.

Ways et al. teach and claim a method for treating autoimmune diseases, including SLE, associated with B cell activation by inhibiting PKC (see entire document, especially claims 13 and 14).

Ways et al. also teach that inhibiting PKC can inhibit the activation of B cell responses mediated through cross linking of the BcR by blocking the downstream effects of the signaling cascade initiated by BcR cross linking (see "Background of the Invention", especially column 2, lines 1-5). Ways et al. also teach that B cell activation involves reorganization of membrane bound Igs, B cell clonal expansion due to proliferation of the B cells, and the production of antibodies form activated B cells that differentiate into antibody-secreting cells (e.g., column 8). Finally, Ways et al. teach that aberrant B cell activation is involved in autoimmune disease including SLE (e.g., column 8, 5th paragraph).

Ways et al. do not teach a method of desensitizing a BcR by contacting the receptor with a regulatory compound that causes a dissociation of and/or inhibits the association of the extracellular ligand binding component and the transducer component.

Nakamura et al. have been discussed supra and teach an anti-Igβ (CD79b) antibody regulatory compound. Nakamura et al. also teach that regulatory compounds such as antibodies to the BcR transducer components Igβ (also known as CD79b) and/or Igα (also known as CD79a) have potential for therapeutic application in any situation in which it is desirable to suppress humoral immunity (i.e., antibody production) in a patient (see entire document, especially last two paragraphs on page 45). Importantly, Nakamura et al. teach that antibodies to the transducer components (e.g., CD79b) would be particularly desirable for *in vivo* use since they would be expected to be more efficacious than antibodies to the extracellular ligand binding domain (see both the "Introduction" and "discussion", especially page 40, 1st paragraph). Finally, Nakamura et al. teach that it is important to suppress humoral immunity in autoimmune diseases, such as SLE (see last paragraph, page 45).

As also discussed supra, Vilen et al. teach a method of desensitizing a BcR. Vilen et al. provide a brief and partial summary of what was known in the art in 1997 about the molecular details of the signal transduction pathway leading to activation of the B cell after ligand binding to the BcR (see entire document, especially the 2nd paragraph of the introduction). Vilen et al. further address the molecular events involved in receptor desensitization, and teach that the event is proximal to the receptor and results in an uncoupling of the receptor from the signal transduction pathway (see entire document, especially the Discussion on pages 241-242). Vilen et al. further discuss that long-term B cell unresponsiveness is independent of PKC, although PKC can mediate a short-term unresponsiveness (see introduction, 1st paragraph).

Given the teachings of the references, it would have been obvious to a person of ordinary skill in the art to substitute the antibody of Nakamura et al. for the PKC inhibitor of Ways et al. in methods of desensitizing an autoreactive B cell receptor in a patient with the autoimmune disease SLE. As taught by Nakamura, the ordinary artisan would have been motivated to make this substitution because regulatory compounds which bind the transducer component would be particularly desirable for therapeutic applications *in vivo*. As taught by Vilen et al., clearly the ordinary artisan at the time the invention was made did recognize that receptor desensitization was due to the uncoupling of the receptor from the signal transduction pathway; that PKC is a downstream event in the signal transduction pathway; but that the PKC branch of the BcR signaling pathway is only involved in a short-term, rather than long-term form of B cell unresponsiveness.

Clearly Ways et al., Nakamura et al. and Vilen et al. provide sufficient teachings that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention, even without knowledge of the detailed mechanism of action or a full characterization of the signaling cascade. Nakamura et al. teach the regulatory compound used in contacting the BcR. Ways et al. teach a highly desirable endpoint as a functional consequence of inhibiting the BcR signaling cascade. That PKC acts downstream (distal to the BcR) in the signaling cascade was well known in the art at the time the invention was made, as evidenced by the references. Therefore the ordinary artisan at the time the invention was made would have certainly recognized that a regulatory compound such as the antibody of Nakamura et al. that acted upstream (proximal to the BcR) in the signal transduction pathway would be more efficacious than an inhibitor of PKC in blocking B cell activation, and so would have been motivated to substitute the antibody for the PKC inhibitor.

With respect to different forms and fine specificities of antibodies, modification of antibodies having a desired specificity such as for a transducer component was routinely practiced by the ordinary artisan at the time the invention was made in order to obtain antibodies with particular characteristics such as improved therapeutic potential. Thus various forms of antibodies, including monovalent antibodies, are obvious variants once an antibody with the desired antigen specificity has been generated. Furthermore, the production of antibodies (in any of a variety of forms) to any specific site on a known antigen (such as either Igα or Igβ) was of itself a matter of routine experimentation for the ordinary artisan at the time the invention was made, as evidenced by the anti-CD79b (Igβ) antibody of Nakamura et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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